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Review

Effects of multidomain interventions on health outcomes in older adults: A systematic review and meta-analysis

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ABSTRACT

Background: With rising global aging, healthcare systems face challenges from multimorbidity, functional decline, and cognitive impairment. Multidomain interventions offer a promising approach to promoting healthy aging. This systematic review and meta-analysis evaluated the effects of multidomain interventions (≥3 domains) on motor-functional, cognitive, and psychological outcomes in older adults without moderate/severe dementia.

Methods: Following PRISMA guidelines, PubMed and Embase were searched up to April 30, 2024. Eligible studies included clinical trials or observational studies involving adults ≥60 years receiving multidomain interventions versus control/standard care. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated.

Results: Thirty-eight studies (57 comparisons) were included (median age: 75.3 intervention, 75.1 control; >60% female). Intervention lasted 2–36 months (median 6.0). All studies targeted the physical domain, 78.9% cognitive, 81.6% nutritional, and 84.2% additional domains. Motor-functional outcomes improved significantly (e.g., Short Physical Performance Battery: SMD = 0.40, 95% CI 0.14 to 0.66; Cardiovascular Health Study frailty criteria: SMD = −0.14, 95% CI −0.23 to −0.05), with diminishing effects over time. Other indicators (e.g., handgrip strength), showed modest improvements. Cognitive improvements were limited to Montreal Cognitive Assessment (MoCA; SMD = 0.23, 95% CI 0.06 to 0.40). Psychological benefits included reduced depressive symptoms (Geriatric Depression Scale: SMD = −0.35, 95% CI −0.57 to −0.12). Effect estimates for Timed Up and Go and RBANS were attenuated in sensitivity analysis excluding high-risk-of-bias studies.

Conclusions: Multidomain interventions improve motor-functional and psychological well-being. Moderate cognitive benefits are observed primarily using the MoCA. These findings support large-scale implementation in geriatric care and highlight the need for strategies to sustain long-term effectiveness.

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1. Introduction

As the global population ages rapidly, healthcare systems are increasingly strained by the rising prevalence of age-related conditions such as multimorbidity, frailty, and functional and cognitive decline. The coexistence of these conditions substantially increases clinical complexity and is associated with poorer health outcomes and disability, rendering single-disease-oriented interventions and conventional care models inadequate and costly [1–4]. This growing burden underscores the need for scalable and sustainable solutions to preserve independence and enhance well-being in aging populations [5]. A multidimensional approach is therefore essential to address age-related health challenges effectively. Multidomain interventions—targeting multiple health domains simultaneously (e.g., physical, cognitive, psychological, and nutritional)—may offer an effective strategy for improving health outcomes in older adults [6–9].

However, current evidence for multidomain interventions remains heterogeneous. Previous systematic reviews and meta-analyses have primarily examined combinations of two interventions (usually physical exercise and nutrition) or have been limited to specific populations, such as pre-frail individuals [7,10–12]. Others have assessed interventions targeting a single outcome measure, such as cognition or mood [13–15]. Therefore, further research is needed to determine the effectiveness of multidomain interventions and identify the specific health outcomes most impacted.

This systematic review and meta-analysis aims to evaluate the effects of multidomain interventions in older adults without moderate or severe dementia, targeting at least three domains and reporting data on motor-functional, cognitive, and psychological outcomes.

2. Methods

2.1. Data sources and searches

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16] guidelines, PubMed and Embase were systematically searched from inception to April 30, 2024, using medical subject headings (MeSH) terms and free-text keywords. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD420261358505).

2.2. Study selection

Inclusion criteria were defined according to the PICOS format (Population, Interventions, Comparator, Outcome, Study design), as detailed in eTable 1 of the Supplement: i) participants were older adults (mean age ≥60 years); ii) the intervention group underwent a multidomain intervention targeting ≥3 domains; iii) the control group maintained usual lifestyle practices or standard care; iv) outcomes included motor-functional, cognitive, or psychological measures; and v) the study design was either a clinical trial or observational study. Only publications in English were considered.

Studies which did not meet the inclusion criteria, or those focusing exclusively on participants with moderate or severe dementia or major depression, were excluded.

Where multiple publications originated from the same study, only the most recent was included.

Authors with diverse expertise (neurologists, geriatricians, and statisticians) independently screened titles and abstracts using the web tool Rayyan [17] and the validated artificial intelligence software ASReview [18].

2.3. Data extraction and quality assessment

Data extraction followed a predefined form, reporting: first author, year of publication, setting (community, hospital, assisted living facility), country, study design, sample size, population characteristics, study arms, mean age and female proportion in intervention and control groups, intervention duration (months), types and details of interventions in both groups, outcome types and descriptions, measurement tools, and pre- and post-intervention results expressed as means and standard deviations (SDs) or as within-group mean differences with corresponding SDs.

Risk of bias was independently assessed by two authors (one neurologist and one geriatrician) using the latest version of the Cochrane Risk of Bias tool (RoB 2) [19]. Each RoB 2 bias domain was rated as having a “low risk of bias”, “some concerns”, or “high risk of bias”. Any discrepancies were resolved through discussion between the two authors.

2.4. Data synthesis and analysis

Outcomes were categorized as motor-functional, cognitive, or psychological, following established definitions. This categorization reflects the multidimensional nature of health determinants in older adults, according to the World Health Organization [5].

Motor-functional outcomes included activities of daily living (ADLs) and instrumental activities of daily living (IADLs) [20,21], as well as performance-based assessments such as the Short Physical Performance Battery (SPPB) [22] and Cardiovascular Health Study (CHS) frailty criteria. Additional indicators comprised muscle strength (e.g., handgrip strength), endurance (e.g., walking speed), balance (e.g., Timed Up and Go, TUG, test), daily step count, Moderate-to-Vigorous Physical Activity (MVPA), Leisure-Time Physical Activity (LTPA), and Five Times Sit to Stand Test (FTSST). These outcomes were selected for their relevance to physical resilience and their prognostic value in aging populations [23, 24].

Cognitive outcomes encompassed both global cognition and specific domains (i.e., memory, attention, and executive function) assessed through standardized tools including the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), Trail Making Test-A and -B (TMT-A and TMT-B), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). These tools are recognized for their validity in detecting cognitive decline [25].

Psychological outcomes, addressing emotional well-being, depressive symptoms, and anxiety, were assessed using validated measures such as the Geriatric Depression Scale (GDS) and the Center for Epidemiologic Studies Depression scale [26].

Multi-arm studies were treated as separate comparisons and only outcomes reported in at least three publications were analyzed. Where the SD for a within-group difference was missing, a correlation of 0.5 between pre- and post-intervention measurements was assumed.

Heterogeneity was assessed using the Q test. The I^2 statistic indicating the proportion of variability due to heterogeneity was also calculated. An I^2 >50% was considered to reflect significant heterogeneity [27]. For outcomes with an I^2 ≤50%, a fixed effect model was applied; otherwise, random-effects estimates were reported. Between-study variance (τ^2) was estimated using the DerSimonian and Laird approach. A conservative approach was adopted for highly heterogeneous outcomes, particularly those reported in a limited number of studies with similar sample sizes. The Hartung-Knapp method was applied to adjust test statistics and confidence intervals (CIs); the Sidik-Jonkman method was used to estimate τ^2 [28]. The pooled effect size comparing intervention and control groups was reported as the standardized mean difference (SMD) with 95% CI. Sensitivity analyses included re-estimating pooled effects, assuming a 0 correlation between pre- and post-intervention measurements, and excluding publications at high risk of bias. Subgroup meta-analyses were conducted by outcome measurement timing. For outcomes with at least 10 estimates, publication bias was assessed using funnel plots and the Egger’s regression test p-value.

Analyses were performed using SAS v. 9.4 (SAS Institute, Cary, NC) and R v. 4.0.2.

3. Results

3.1. Study selection

A total of 19,825 non-duplicate records were identified, of which 19,613 were excluded during title and abstract screening. One record identified in a systematic review was added to the list of full-text articles for eligibility. Following full-text screening, 175 articles were excluded, resulting in 38 included articles (57 comparisons; Fig. 1) [9,29–65].

3.2. Study characteristics

Table 1 summarizes study characteristics (detailed in eTable 2).

Publication years spanned from 1998 to 2024, with 81.6% of studies published after 2010. Most studies (92.1%) were conducted in community settings (with one study also recruiting from assisted living facilities); three studies were in hospital settings. All studies were clinical trials, mainly randomized (89.5%). The majority were conducted in Europe (39.5%) and Asia (36.8%), with 18.4% in America and 5.3% in Oceania. Intervention durations spanned 2–36 months (median 6.0; interquartile range, IQR, 5.5−15.0). Median sample size was 263 (IQR 152−733). Median age was 75.3 years in intervention groups and 75.1 years in control groups, with median female proportions of 62.9% and 61.2%, respectively.

All studies targeted the physical domain, defined as interventions aimed at reducing disability and improving physical performance. A total of 30 studies (78.9%) included the cognitive domain, 31 (81.6%) the nutritional domain, and 32 additional domains (e.g., social activities, management of metabolic indicators and vascular risk factors, medication management, fall prevention, etc.). Overall, 15 studies targeted three domains, 17 four domains, and 6 five or more domains (eTables 2 and 3).

3.3. Risk of bias assessment

Overall study quality was high, with only 10% classified as “high risk of bias” (eFig. 1).

3.4. Outcome measures

eTable 4 lists the 55 reported outcomes, categorized into motor-functional, cognitive, and psychological measures. Notably, 32 outcomes (58.2%) were reported in only one study. Meta-analysis was conducted on outcomes reported in at least three studies.

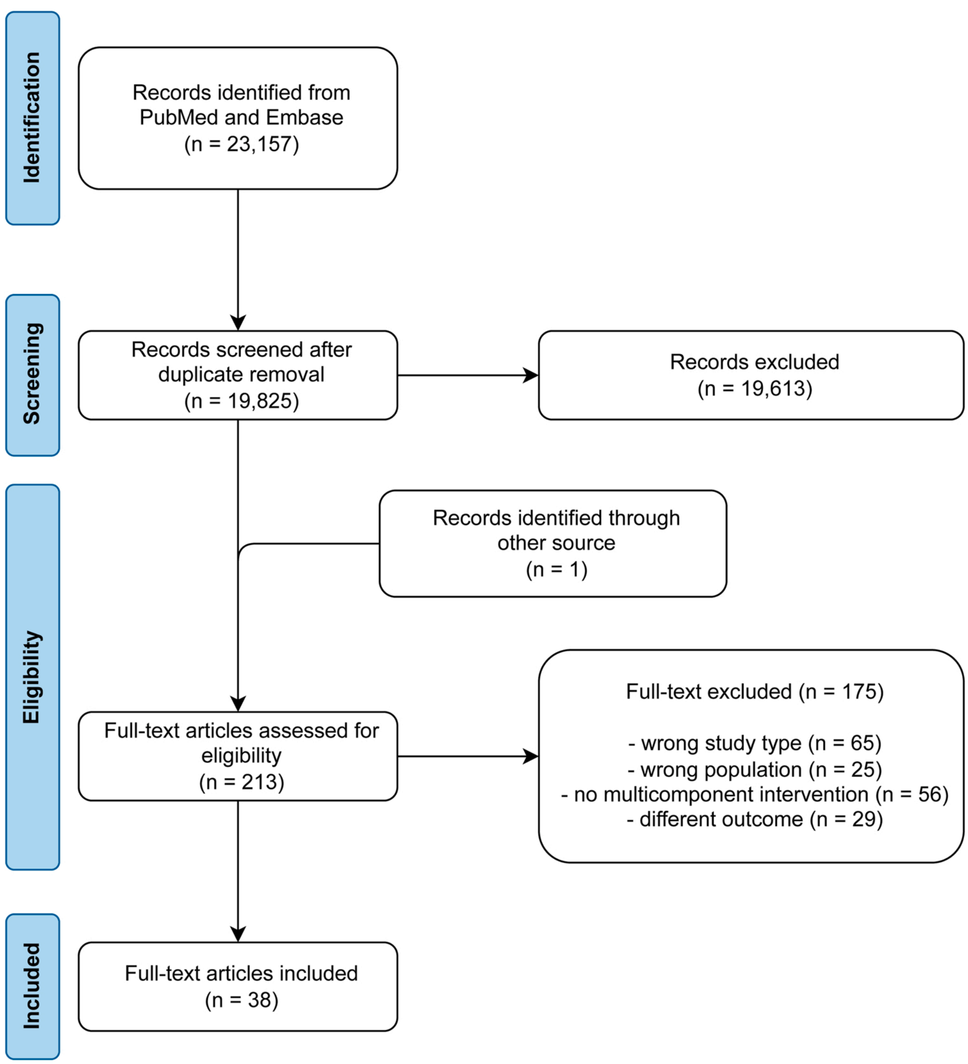

Fig. 1. Study flow diagram.

Table 1
Characteristics of included publications.

	Total (*N* = 38)	
	N	%
Setting		
Community-dwelling	34	89.5
Community-dwelling or assisted living facility	1	2.6
Hospital	3	7.9
Country		
Europe	15	39.5
Asia	14	36.8
America	7	18.4
Oceania	2	5.3
Study design		
RCT	34	89.5
Non-randomized CT	4	10.5
N studies with intervention on physical domain	38	100.0
N studies with intervention on cognitive domain	30	78.9
N studies with intervention on nutritional domain	31	81.6
N studies with at least one intervention on *other* domains	32	84.2
Social activities	15	
Management of metabolic indicators and vascular risk factors	9	
Medication management	8	
Health education	6	
Falls prevention	5	
Mindfulness	2	
Motivational enhancement	1	
Duration of intervention (months), median (IQR)	6.0 (5.5–15.0)	
Number of patients enrolled, median (IQR)	263 (152–733)	
Mean age		
Intervention group, median (IQR)	75.3 (71.2–79.5)	
Control group, median (IQR)	75.1 (73.1–78.5)	
Percentage of females enrolled		
Intervention group, median (IQR)	62.9 (53.1–72.5)	
Control group, median (IQR)	61.2 (52.8–69.7)	

Abbreviations: IQR, interquartile range; RCT, randomized controlled trial.

3.5. Meta-analysis results

3.5.1. Motor-functional outcomes

Eight studies (twelve estimates) reported handgrip strength and walking speed, showing low heterogeneity and modest benefit of multidomain interventions compared with controls (pooled SMD = 0.07, 95% CI 0.01 to 0.13, $I^2 = 35\%$ for handgrip strength; SMD = 0.08, 95% CI 0.02 to 0.14, $I^2 = 0\%$ for walking speed; Fig. 2, eFig. 2). Subgroup analysis showed greater improvements for handgrip strength when measured within 6 months (SMD = 0.11) compared with measurements after 6 months (SMD = 0.03), although not statistically significant (p-value = 0.24 for subgroup differences). A similar pattern was reported for walking speed (SMD = 0.09 vs 0.07, p-value = 0.80; eFig. 5).

SPPB was reported in seven studies (nine estimates), showing significant improvement in the intervention group compared with controls (SMD = 0.40, 95% CI 0.14 to 0.66, $I^2 = 93\%$; Fig. 2, eFig. 2). Subgroup analysis indicated that studies with assessment within 6 months demonstrated a significantly larger effect (SMD = 0.63) than those with assessment after 6 months (SMD = 0.12, p-value = 0.03). Nevertheless, substantial heterogeneity persisted in both subgroups (87% and 84%, respectively; eFig. 5).

Daily step count (three estimates), LTPA (seven estimates), MVPA (four estimates), and FTSST (four estimates) showed greater improvement in the intervention than in the control group (SMDs = 0.31, 0.14, 0.18, and −0.13, respectively, $I^2 = 0\%$). The TUG test (five studies, six estimates; SMD = −0.65, 95% CI −1.23 to −0.06, $I^2 = 95\%$) and CHS frailty criteria (four studies, seven estimates; SMD = −0.14, 95% CI −0.23 to −0.05, $I^2 = 38\%$; Fig. 2, eFig. 2) also favored the intervention group.

The assessment of ADLs and IADLs revealed substantial heterogeneity in both the tools and scoring methods used, which prevented data pooling for meta-analysis (eTable 5). Using the Bayer ADL scale (higher scores indicating poorer performance), Moon et al. [39] reported smaller declines in facility-based and home-based intervention groups (mean = −0.30, SD = 0.90; mean = −0.13, SD = 0.66; respectively) compared with controls (mean = 0.11, SD = 1.12). However, these differences did not reach statistical significance. Using a 6-item ADL index, Gitlin et al. [64] reported significantly better outcomes in the intervention group compared with controls (mean = −0.24, SD = 0.56 vs mean = −0.10, SD = 0.62; p-value = 0.04). Similarly, Gené Huguet et al. [63] assessed functional performance with the Barthel Index (BI), finding significant improvement in the intervention group. Conversely, Cameron et al. [51] observed a decline in BI scores, with a less pronounced reduction in the intervention group compared with controls, although the between-group difference was not statistically significant. Regarding IADLs, three studies using the Lawton and Brody IADL scale or its derivatives reported modest improvements in the intervention group; however, none of these differences reached statistical significance compared with controls.

3.5.2. Cognitive outcomes

The MMSE (five estimates), TMT-B (five estimates), and TMT-A (four estimates) showed no improvement with multidomain intervention (SMDs = 0.05, 0, and 0.06, respectively; $I^2 \leq 37\%$). Conversely, four studies using the MoCA (seven estimates) showed a mild benefit (SMD = 0.23, 95% CI 0.06 to 0.40, $I^2 = 55\%$); those using the RBANS (three studies, four estimates) suggested improvement, although not statistically significant (SMD = 0.42, 95% CI −0.05 to 0.88, $I^2 = 59\%$; Fig. 2, eFig. 3).

3.5.3. Psychological outcomes

The eight studies using the GDS (ten estimates) reported a greater reduction in depressive symptoms in the intervention group compared with controls (SMD = −0.35, 95% CI −0.57 to −0.12, $I^2 = 88\%$; Fig. 2, eFig. 4).

3.6. Sensitivity analysis and publication bias

Sensitivity analysis confirmed the primary findings of this work (eFig. 6). When high risk of bias studies were excluded, the results for walking speed, SPPB, daily step count, FTSST, MMSE, and GDS remained consistent; the estimates for TUG and RBANS became imprecise and statistically non-significant (eFig. 7). Funnel plots showed no asymmetry for handgrip strength (Egger's test p-value = 0.88) and walking speed (p-value = 0.49), but suggested publication bias for GDS (p-value = 0.03; eFig. 8).

4. Discussion

This is the first systematic review and meta-analysis comprehensively evaluating the effects of multidomain interventions targeting at least three predefined domains on a broad range of health outcomes, including motor-functional, cognitive, and psychological measures, in older adults without moderate or severe dementia or major depression. In the 38 reviewed studies published between 1998 and 2024, multidomain interventions were effective across all outcomes, with the strongest effects observed in motor-functional and psychological measures. However, effectiveness was more pronounced in the short term and declined over time. These findings highlight the role of multidomain interventions in promoting healthy aging, emphasizing the need for strategies to enhance long-term adherence and optimize the selection of intervention domains.

Motor-functional improvements were consistently observed, particularly when assessed using the SPPB. This tool proved a reliable indicator of functional gains, with significant benefits noted during the

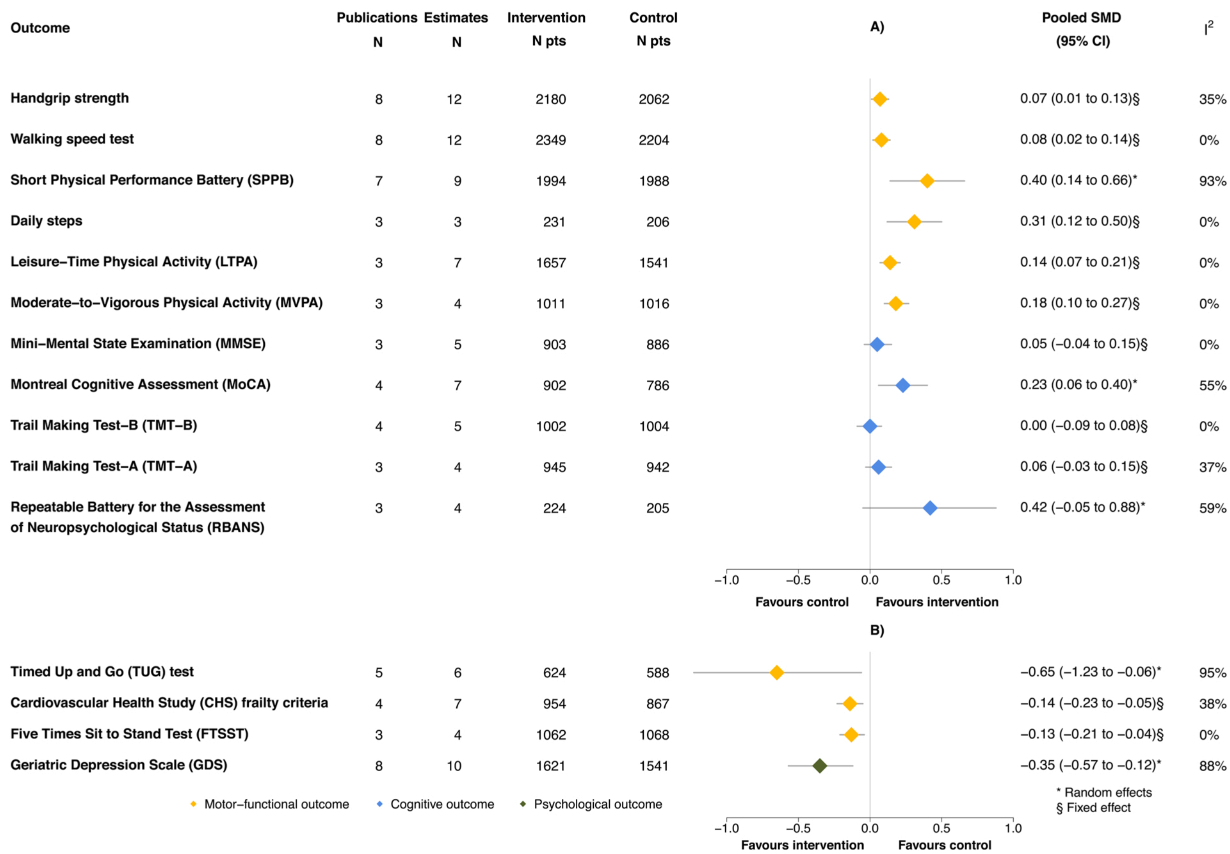

Fig. 2. Forest plot showing summary meta-analytical results for the selected outcomes.
Diamonds indicate the meta-analytic pooled standardized mean difference (SMD). Horizontal lines indicate the 95% confidence intervals (CI). The solid vertical line indicates a pooled SMD of 0, which is the null-hypothesis value (i.e., no association between multidomain intervention and change in the selected outcome). In panel A) values greater than zero indicate intervention is better than control; in panel B) values lower than zero indicate intervention is better than control. Yellow diamonds refer to motor-functional outcomes, blue diamonds to cognitive outcomes, and the green diamond to the psychological outcome.

initial months of intervention (pooled SMD $= 0.63$ at ≤ 6 months). However, the effects diminished over time, raising critical concerns about long-term adherence and retention. Strategies such as structured "recall" programs, motivational interventions, and periodic booster sessions could help maintain participation and enhance program effectiveness over time, particularly by supporting adherence and reinforcing behavioural changes beyond the active intervention phase [66]. Additionally, sex-specific differences in adherence and outcomes warrant further investigation, as understanding these variations could inform the conceptualization of tailored programs to maximize effectiveness and inclusivity [67].

Improvements were observed in other motor-functional outcomes such as daily step count, LTPA, MVPA, and FTSST. However, gains in handgrip strength were not sustained over time. Interestingly, gait speed, which depends on a complex interplay of cardiovascular function, balance, and muscle strength, showed limited improvement, suggesting the need for more targeted approaches to address its multifaceted nature [68,69].

The findings on the impact of multidomain interventions on cognition also warrant further attention, as benefits were observed only when assessed using the MoCA; assessments using the MMSE, TMT-A, TMT-B, or RBANS showed no significant effects. This discrepancy likely reflects differences in measurement sensitivity between instruments. The MoCA has been shown to be more sensitive to subtle cognitive changes in individuals who still perform within the normal range on the MMSE [70]. In contrast, the MMSE is characterized by a pronounced ceiling effect in higher-functioning individuals, which limits its ability to detect mild deficits and to capture intervention-related improvements [71]. The lack of effectiveness with RBANS may stem from the small number of studies using this tool ($n = 3$). Additionally, the heterogeneity of participant cognitive status, ranging from normal cognition to mild dementia, may have influenced the results.

Multidomain interventions also demonstrated benefits in psychological outcomes, as measured by the GDS, with a pooled SMD of −0.35 favoring the intervention group, albeit with marked heterogeneity across studies.

Nevertheless, it is important to reflect on the type and quality of the studies included in this systematic review and meta-analysis. Intervention protocols varied widely and were highly study-specific. For instance, in the MAPT trial [29,46,59], group counseling and/or training sessions were conducted twice a week during the first month, then reduced to once a week in the second month. In contrast, Bae et al. [40] administered sessions twice a week over 24 weeks. Chen et al. [60] implemented a more staggered approach, administering sessions once a week in the first month, twice a month in the second month, and once a month in the third month. Additionally, in 25 studies (65.8%), the control group received usual care; in the study by Moon et al. [39] participants received usual care alongside educational material on dementia prevention. In 10 studies (26.3%), health education classes or advice were provided. Considering the heterogeneity of the intervention protocols, an important question is whether the observed benefits are truly attributable to these interventions per se, or to specific components driving the effect. According to a recent network analysis from Mendes et al. [72], selected combinations (particularly physical exercise and cognitive training) appear to account for a substantial proportion of the observed benefit, whereas increasing the number of domains does not necessarily translate into greater effectiveness. Hence, effectiveness may depend less on the number of domains and more on the target integration, intensity, and sustained delivery of key components. This shifts the focus from “more domains” to “better-designed combinations,” with important implications for scalability and clinical implementation.

Despite the broad geographical representation of the included trials (comprising multiple continents), most studies were conducted in high-income countries, where resources for implementation are more readily available. This underscores the need for further research in low- and middle-income countries, where aging populations are growing most rapidly [73]. Cultural and nutritional differences, along with resource constraints, may influence the effectiveness of these interventions, making this another key area for future investigation.

Moreover, the generalizability of these findings across care settings represents a key issue. Most studies were conducted in community-dwelling populations, which may limit direct applicability to hospitalized or post-acute patients. However, acute care settings may represent a critical window for intervention, given the risk of functional decline associated with hospitalization. In this context, multidomain interventions may be particularly relevant, although their implementation requires adaptation to ensure feasibility and integration within routine care pathways. Ongoing initiatives evaluating multidomain interventions across community, hospital, and long-term care settings are expected to provide further insights into their scalability and sustainability [74].

Overall, these findings suggest potentially relevant clinical and organizational implications across the continuum of care for older adults, although evidence remains heterogeneous. For instance, recent trials such as AgeWell.de [75], conducted in individuals at increased risk of dementia, did not demonstrate consistent cognitive benefits, possibly influenced by contextual factors including recruitment challenges and intervention intensity. In contrast, more recent evidence from large-scale initiatives such as the U.S. POINTER study [76] and long-term follow-up from the FINGER trial [77] supports the potential of multidomain approaches, while also underscoring the importance of sustained engagement and adherence over time.

Taken together, these findings call for greater standardization and refinement of multidomain intervention models, particularly regarding target populations, intervention components, and delivery strategies. Rather than a one-size-fits-all approach, future efforts should focus on tailoring interventions to specific clinical contexts and ensuring feasibility across different care settings.

In this perspective, multidomain interventions may represent a promising strategy to support healthy aging, potentially contributing to the prevention of functional decline, cognitive impairment, and depressive symptoms. However, their large-scale implementation should be approached cautiously and supported by further evidence on effectiveness, sustainability, and cost-effectiveness.

In primary care, existing infrastructures could offer an opportunity to deliver community-based multidomain programs, particularly through screening and personalized preventive pathways. In secondary and tertiary care settings, these interventions might complement disease-specific treatments and rehabilitation strategies, although their integration into routine practice requires further evaluation [78].

4.1. Strengths and limitations

The major strengths of this meta-analysis are its rigorous methodology, the high number of included studies, and the application of sensitivity analyses. The comprehensive and representative nature of the evidence highlights the benefits of implementing these strategies globally.

Limitations include the sparse number of studies in secondary and tertiary care settings, restricting the ability to evaluate differences across settings, as well as the variations in intervention domains and durations, which may have affected the results. Furthermore, it remains uncertain whether multidomain interventions would be similarly effective in populations with moderate or severe dementia. In addition, for outcomes with fewer than 10 estimates, publication bias could not be formally assessed; therefore, these findings should be interpreted with caution.

5. Conclusions

In conclusion, this meta-analysis demonstrates the efficacy of multidomain interventions across care settings, supporting their integration into routine care to address early aging-related decline, improve health outcomes, and bridge preventive and therapeutic approaches. These findings highlight the potential of multidomain interventions as a cornerstone of healthcare policy.

CRediT authorship contribution statement

Conception and design: CF, GB, AZ, GS, VS.
Data acquisition: EP, CO, LC, CC, VD, AP, AZ.
Statistical data analysis: EP, AP, AZ.
Interpretation of results and manuscript writing: EP, CO, AMO, AF, FEP, MCF, GB, AZ.
Final approval of manuscript: All authors.
Accountable for all aspects of the work: All authors.
The principal investigators (EP, CO, AZ, GB, CF) had full access and verified all the data in the study and had final responsibility for the decision to submit for publication.

Ethics approval and consent to participate

Not applicable.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used an AI-assisted technology, specifically the validated software ASReview, during the screening phase. ASReview supports the screening process by prioritizing records from the most likely to least likely to be included, based on prior knowledge provided by the researcher. In addition, generative AI-assisted tools were used during the preparation of the manuscript for language refinement, clarity, and stylistic improvement. No analytical or interpretative content was generated by these tools. Following their use, the authors carefully reviewed and edited the manuscript as necessary and take full responsibility for its content.

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Sponsor’s role

This work was conducted independently of the funders, who had no influence over the study design, data collection and analysis, manuscript writing, or publication decision.

Transparency

The lead authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination

We plan to disseminate the findings and conclusions from this study through a lay language summary of our findings, which will be widely promoted by our respective institutions through press releases, social media, and the websites of our institutions. We also plan to present the results of our study at international scientific conferences.

Availability of data and materials

Detailed extracted data on all included studies are available upon reasonable request to the corresponding author.

Declaration of competing interest

All authors declared: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

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Appendix A. Supplementary data

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